Use of a mouse in vitro fertilization model to understand the developmental origins of health and disease hypothesis.

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Public Summary:
The Developmental Origins of Health and Disease hypothesis holds that alterations to homeostasis during critical periods of development can predispose individuals to adult-onset chronic diseases such as diabetes and metabolic syndrome. It remains controversial whether preimplantation embryo manipulation, clinically used to treat patients with infertility, disturbs homeostasis and affects long-term growth and metabolism. To address this controversy, we have assessed the effects of in vitro fertilization (IVF) on postnatal physiology in mice. We demonstrate that IVF and embryo culture, even under conditions considered optimal for mouse embryo culture, alter postnatal growth trajectory, fat accumulation, and glucose metabolism in adult mice. Unbiased metabolic profiling in serum and microarray analysis of pancreatic islets and insulin sensitive tissues (liver, skeletal muscle, and adipose tissue) revealed broad changes in metabolic homeostasis, characterized by systemic oxidative stress and mitochondrial dysfunction. Adopting a candidate approach, we identify thioredoxin-interacting protein (TXNIP), a key molecule involved in integrating cellular nutritional and oxidative states with metabolic response, as a marker for preimplantation stress and demonstrate tissue-specific epigenetic and transcriptional TXNIP misregulation in selected adult tissues. Importantly, dysregulation of TXNIP expression is associated with enrichment for H4 acetylation at the Txnip promoter that persists from the blastocyst stage through adulthood in adipose tissue. Our data support the vulnerability of preimplantation embryos to environmental disturbance and demonstrate that conception by IVF can reprogram metabolic homeostasis through metabolic, transcriptional, and epigenetic mechanisms with lasting effects for adult growth and fitness. This study has wide clinical relevance and underscores the importance of continued follow-up of IVF-conceived offspring.

Scientific Abstract:
The Developmental Origins of Health and Disease hypothesis holds that alterations to homeostasis during critical periods of development can predispose individuals to adult-onset chronic diseases such as diabetes and metabolic syndrome. It remains controversial whether preimplantation embryo manipulation, clinically used to treat patients with infertility, disturbs homeostasis and affects long-term growth and metabolism. To address this controversy, we have assessed the effects of in vitro fertilization (IVF) on postnatal physiology in mice. We demonstrate that IVF and embryo culture, even under conditions considered optimal for mouse embryo culture, alter postnatal growth trajectory, fat accumulation, and glucose metabolism in adult mice. Unbiased metabolic profiling in serum and microarray analysis of pancreatic islets and insulin sensitive tissues (liver, skeletal muscle, and adipose tissue) revealed broad changes in metabolic homeostasis, characterized by systemic oxidative stress and mitochondrial dysfunction. Adopting a candidate approach, we identify thioredoxin-interacting protein (TXNIP), a key molecule involved in integrating cellular nutritional and oxidative states with metabolic response, as a marker for preimplantation stress and demonstrate tissue-specific epigenetic and transcriptional TXNIP misregulation in selected adult tissues. Importantly, dysregulation of TXNIP expression is associated with enrichment for H4 acetylation at the Txnip promoter that persists from the blastocyst stage through adulthood in adipose tissue. Our data support the vulnerability of preimplantation embryos to environmental disturbance and demonstrate that conception by IVF can reprogram metabolic homeostasis through metabolic, transcriptional, and epigenetic mechanisms with lasting effects for adult growth and fitness. This study has wide clinical relevance and underscores the importance of continued follow-up of IVF-conceived offspring.